Cardiovascular Topics

Progressive familial heart block type II (PFHBII): a clinical profile from 1977 to 2003

P. FERNANDEZ, V.A. CORFIELD, P.A. BRINK

Summary

An evaluation of a 38-year-old Caucasian woman, who was referred to Tygerberg Hospital (Western Cape Province, RSA) with Wenckebach second-degree or possibly complete atrioventricular (AV) block that had progressed from first-degree AV block, identified a family history of the cardiac conduction system disorder progressive familial heart block type II (PFHBII). This prompted a retrospective clinical review of the subjects described in the original study, as well as additional family members who had not been examined in the original study.[1] Progression of clinical features was observed, but more importantly, PFHBII was clinically redefined as an AV nodal disorder, which may progress to dilated cardiomyopathy (DCM).

Cardiovasc J South Afr 2004; 15: 129–132. www.cvjsa.co.za

In January 2003, a 38-year-old Caucasian woman with Wenckebach second-degree or possibly complete atrioventricular (AV) block and a heart rate of 43 beats per minute (bpm) (Fig. 1) (Table I, individual IV:20) was admitted to the Cardiology Unit of Tygerberg Hospital (Western Cape Province). The subject had been examined previously (P.A. Brink, May 2000) and diagnosed with first-degree AV block with a P–R interval of 240 milliseconds (Fig. 2). Genealogy studies indicated that the subject was the daughter of the index case of the previously described South African family with progressive familial heart block type II (PFHBII).[1]

In 1977, Brink and Torrington characterised PFHBII as an inherited autosomal dominant cardiac conduction system disorder, which segregated in a South African Caucasian Afrikaner family from the Eastern Cape Province.[1] The ECG features of PFHBII were at that time defined by isolated sinus bradycardia (SB), isolated left posterior hemiblock (LPHB) or complete heart block (CHB) with narrow QRS complexes. In this report, we describe a retrospective study of the family members examined by Brink and Torrington in 1977. Clinical data are also presented of additional subjects from the same family who were not examined in the original study. The results of the study reiterated the progressive nature of the disorder and prompted a redefinition of the clinical profile of PFHBII.

US/MRC Centre for Molecular and Cellular Biology, Faculty of Health Sciences, University of Stellenbosch, Tygerberg

P. FERNANDEZ, B.Sc. Hons.
V.A. CORFIELD, Ph.D.

Department of Internal Medicine, Faculty of Health Sciences, University of Stellenbosch and Tygerberg Hospital, Tygerberg

P.A. BRINK, M.D., Ph.D.

Fig. 1. Twelve-lead ECG strip for individual IV:20, taken in January 2003, showing a slow, irregular sinus rhythm with no consistent ventricular response. The AV nodal delay could represent a Wenckebach phenomenon or alternately, complete AV dissociation. The subject subsequently had a pacemaker implanted.

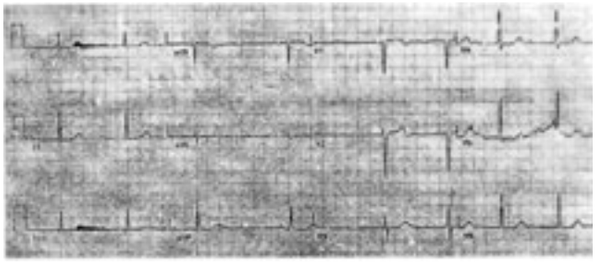

Fig. 2. Twelve-lead ECG strip for individual IV:20, showing first-degree AV block (P–R interval = 240 milliseconds). The ECG was taken in May 2000.

TABLE I. EVALUATION OF FOLLOW-UP CLINICAL DATA OF THE PFHBII FAMILY MEMBERS CLINICALLY ASSESSED IN THE ORIGINAL STUDY

Indidual	*[a]Age (y)*	*ECG*	*EF*	*LVEDD*	*Comment*
III:6	68	normal	76	4.8	unaffected
III:8	**42**	**3° AVB**	**60**	**4.5**	**[b]SB = 48 bpm, CHB (PM 42 y); present age = 69 y**
III:10	64	normal	65	4.4	unaffected
III:12	**37**	**3° AVB**	**41**	**6.3**	**CHB (PM 37 y), DCM, [+]59 y**
IV:9	**41**	**3° AVB**	**42**	**5.7**	**CHB (PM 41 y), DCM, [+]46 y**
IV:11	**35**	**3° AVB**	**nd**	**nd**	**CHB (PM 35 y); present age = 36 y**
IV:14	32	normal	65	4.3	unaffected
[c]IV:16	40	normal	64	4.5	slow R-wave progression; transition to dominant R-wave in V4 – otherwise unaffected
IV:18	33	normal	70	4.7	unaffected
IV:19	31	normal	63	4.9	unaffected
IV:20	**38**	**2° or 3° AVB**	**61**	**5.5**	**1° AVB (P–R interval = 240 m/s, May 2000); SB = 43 bpm, Wenckebach/complete AVB (PM 38 y), January 2003; present age = 38 y**
IV:21	41	normal	64	4.4	unaffected
IV:24	39	normal	60	4.5	unaffected
IV:25	**29**	**3° AVB**	**40**	**5.8**	**CHB (PM 29 y), DCM, [+]43 y**
IV:26	**15**	**nd**	**nd**	**nd**	**heart transplant, DCM, [+]15 y**

Not shown in the table are individuals II:3, III:7, III:9, III:11; IV:12, IV:13, IV:15, IV:17 and IV:22, who were designated clinically unaffected based on family history or a family physician's medical report. No further data could be obtained for these individuals.
[a]Age at examination in years (y); [b]Heart rate prior to pacemaker (PM) implant; [c]Individuals with atypical accompanying features; [+]Age at death
1° = first-degree; 2° = second-degree; 3° = third-degree; AVB = atrioventricular block; bpm = beats per minute; CHB = complete heart block; DCM = dilated cardiomyopathy; EF = ejection fraction; LVEDD = left ventricular end diastolic diameter; m/s = milliseconds; nd = no data available; (PM y) = PM age at implant; SB = sinus bradycardia
Clinically affected individuals are indicated in bold

Methods

Ethical approval

The present study formed part of a project approved by the Ethics Committee of the Faculty of Health Sciences at the University of Stellenbosch.

Genealogy and extent of the disease

The South African Caucasian Afrikaner family presented in this study was previously described.[1] Extensive genealogy studies were performed to determine the segregation of PFHBII in other branches of the family.

Patient panel

Twelve-lead ECG and two-dimensional echocardiographic follow-up examinations were acquired (1977 to present) from Tygerberg Hospital or from the personal physicians of subjects described in the original PFHBII study.[1] Clinical data were also obtained for the children (born after 1977) of these subjects, as well as other available members who were not examined in the original study.[1] Where the records were unavailable, if possible, clinical histories were obtained from the subjects themselves or close relatives. Clinical histories of deceased individuals were also included in the study.

Electrocardiographic and echocardiographic criteria

The ECG diagnostic criteria for PFHBII were previously established.[1] In addition, the study included minimum criteria for an echocardiographic diagnosis of dilated cardiomyopathy (DCM), defined by an ejection fraction of less than 45% and a left ventricular end-diastolic diameter of greater than 5.6 cm in the absence of hypertension and valvular heart disease or a history consistent with ischaemic heart disease. All measurements were made according to the American Society of Echocardiography guidelines.[2]

Results

Genealogy and extent of the disease

The study by Brink and Torrington in 1977 obtained information on 140 members of a South African family, of which 24 members of one family branch were examined by ECG. We performed extensive family studies questioning living first-, second- and third-degree relatives of individual II:2 (Fig. 3) (not including his progeny). Wherever possible, ECGs were performed, and occasionally echocardiographic assessment. We did not detect disease with features of PFHBII, although one third-degree relative had hypertrophic cardiomyopathy. Additionally, we questioned relatives of individual II:3 (Fig. 3) and did not identify evidence of the disease in her lineage. We concluded that individual II:2 was the true carrier of PFHBII (Fig. 3), as his children reported him to have had a heart block. We do not therefore have evidence of segregation of the disease in ancestors or siblings and their progeny of II:2 and II:3, limiting known disease to the current pedigree (Fig. 3).

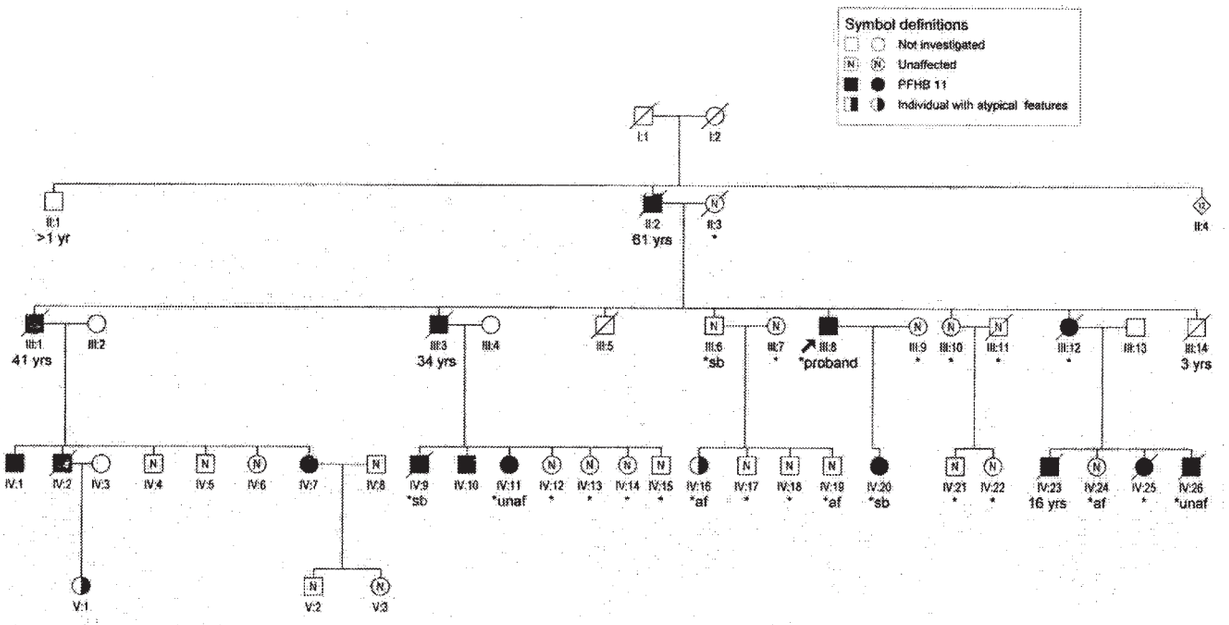

Fig. 3. A family tree showing all kindred of an individual with PFHBII. Squares represent males and circles represent females. An asterisk indicates the individuals examined in the original study. The clinical assessments of subjects whose present diagnoses differ from the original study[1] are shown below the respective symbols (af, subject previously diagnosed as affected; sb, subject previously with sinus bradycardia; unaf, subject previously unaffected).

Clinical data

Twenty-four subjects were assessed in the original study,[1] of whom six were designated clinically affected, and three were identified with SB. Follow-up clinical data or family histories were obtained for the 24 subjects described in the original study[1] (Table I). Our data indicated that two of the three subjects previously identified with SB[1] (Fig. 3, individuals IV:9 and IV:20) subsequently developed AV block and had pacemakers implanted (Table I). Furthermore, three subjects (Fig. 3, individuals III:12, IV:9 and IV:25) showed progression to DCM (Table I). A fourth subject (Fig. 3, individual IV:26), who had previously shown no conduction abnormalities,[1] required a heart transplant as a result of juvenile-onset DCM (Table I). Our follow-up data also differed from the previous diagnoses of three family members. These subjects (Fig. 3, individuals IV:16, IV:19 and IV:24), who had previously been designated clinically affected, presently did not meet our strict diagnostic criteria, although individual IV:16 did present atypical associated features on examination (Table I).

In addition, we obtained clinical or family information for 15 subjects who were not clinically examined in the original study or who were born after 1977 (Fig. 3). Eight of the 15 subjects were assigned a clinically affected status (Table II). Seven of the eight clinically affected individuals developed conduction defects that ranged from atrial fibrillation and CHB to left anterior hemiblock (LAH) (Table II). The eighth affected subject (Table II, individual IV:2) showed progression from AV block to DCM. An additional family member (Table II, individual V:1) presented with atypical features that included severe chest pain with frequent dyspnoea and syncopal episodes. However, the subject has declined to be examined and her clinical status remains uncertain.

Discussion

Evaluation of clinical and family data spanning 26 years confirmed the progression of features in PFHBII. More importantly, the study highlighted the progression to DCM, which was not apparent in the original study. The follow-up study showed that SB preceding CHB occurred frequently in the family, although it must be noted that SB is fairly common in the general population, particularly among athletes.[3] However, upon questioning, most of the affected family members indicated that they had fairly sedentary lifestyles and SB was absent in unaffected subjects with similar living patterns. Therefore, in this family, a slow heart rate of less than 50 bpm is considered familial and a diagnostic criterion of PFHBII.

Generally, individuals with first-degree AV block are asymptomatic and diagnosis thereof is usually incidental. The present study also aimed to identify clinical or physical characteristics occurring in the family that could be indicative of underlying disease. Two subjects with potentially early clinical markers for PFHBII were identified. The first subject (individual IV:16), who was examined in the original study and re-evaluated by us in 2000, was, unlike the previous study, assigned a clinically unaffected status. Our evaluation did indicate a slow R-wave progression, where the transition to a dominant R-wave occurs in V4. A slow R-wave progression is often associated with DCM,[4] although lead placement could also play a role in the ECG assessment. However, we speculate that in this family, the atypical feature could be an early indication of impending

TABLE II. EVALUATION OF CLINICAL DATA OF PFHBII FAMILY MEMBERS WHO WERE NOT CLINICALLY ASSESSED IN THE ORIGINAL STUDY

Indidual	*[a]Age (y)*	*ECG*	*EF*	*LVEDD*	*Comment*
II:2	**61**	**nd**	**nd**	**nd**	**HB (type unknown), [+]61 y**
III:1	**40**	**nd**	**nd**	**nd**	**HR < 50 bpm, CHB (PM 41 y), [+]41 y**
III:3	**45**	**nd**	**nd**	**nd**	**CHB (PM 45 y), failed PM, [+]45 y**
IV:1	**36**	**LAD**	**64**	**4.4**	**LAD (–30º axis), LAH; present age = 41 y**
IV:2	**38**	**3° AVB**	**38**	**6.2**	**[b]SB = 50 bpm, AF, CHB (PM 39 y), DCM, [+]43 y**
IV:4	49	normal	60	4.4	unaffected
IV:5	45	normal	60	4.4	unaffected
IV:6	47	normal	65	4.5	unaffected
IV:7	**33**	**3° AVB**	**52**	**5.1**	**1° AVB (P–R interval = 220 m/s, March 1990), [c]SB = 38 bpm, AF, CHB (PM 33 y, October 1996); present age = 38 y**
IV:8	45	normal	65	4.8	unaffected
IV:10	**36**	**SB**	**nd**	**nd**	**SB = 43 bpm; present age = 39 y**
IV:23	**16**	**3° AVB**	**nd**	**nd**	**CHB (PM 16y), [+]16 y**
[c]V:1	23	nd	nd	nd	chest pain, dyspnoea, syncope
V:3	22	160	63	5.2	unaffected
V:4	20	160	70	4.3	unaffected

[a]Age at examination in years (y); [b]Heart rate prior to pacemaker (PM) implant; [c]Individuals with atypical accompanying features; [+]Age at death
1° = first-degree; 3° = third-degree; AF = atrial fibrillation; AVB = atrioventricular block; bpm = beats per minute; CHB = complete heart block; DCM = dilated cardiomyopathy; LVEDD = left ventricular end diastolic diameter; HB = heart block; HR = heart rate; LAH = left anterior hemiblock; LAD = left axis deviation; EF = ejection fraction; m/s = milliseconds; nd = no data available; (PM y) = PM age at implant; SB = sinus bradycardia
Clinically affected individuals are indicated in bold

cardiac abnormalities. The second subject (individual V:1) had reported severe chest pains, shortness of breath and fainting episodes. Recent correspondence with individual V:1 indicated a persistence of features, despite treatment with Atenolol (P.A. Brink, personal communication). Interestingly, there is a history of sudden death at a relatively young age in the subject's family, with both her grandfather and father (Table II, individuals III:1 and IV:2) having died aged 41 and 43 years, respectively.

The importance of this retrospective study is exemplified by our redefinition of the clinical profile of PFHBII. Barring the one individual with LAH (individual IV:1), we propose that the absence of ventricular conduction delay makes it highly likely that the conduction block occurs close to the origins of the Bundle of His. This suggests that PFHBII is not a disease of the ventricular conduction system. Drawing on observations from ECG data, we have amended the diagnostic criteria and characterise PFHBII as an AV nodal disorder with clinical onset between the fourth and sixth decade. In addition, four family members were identified who progressed from conduction block to DCM (Tables I and II, individuals III:12, IV:2, IV:9 and IV:25). For these subjects, the progression from complete AV block to congestive heart failure (CHF) ranged from five years (individuals IV:2 and IV:9) to 22 and 14 years (individual III:12 and IV:25), respectively. Furthermore, a fifth subject (Table I, individual IV:26) with no prior conduction defects developed DCM in early adolescence. Consequently, these data indicate that in this family, on average, death as a result of CHF occurred before the sixth decade. Unfortunately, the available data did not permit assessing whether the prognosis for individuals who only developed conduction defects was better than for those subjects with DCM. We cannot explain why particular individuals advanced from AV block to DCM, while others only developed conduction defects, but this pattern of clinical features was consistent with other described disorders.[5,6] Consequently, we performed a genetic linkage study and excluded the lamin A/C[5] and CMD1H[6] loci as cause of PFHBII (data not shown).

Conclusions

The data presented emphasise the importance of establishing a family history when making patient diagnoses. The progressive nature of the disorder was reiterated, but more importantly, a familial DCM component was demonstrated in PFHBII. Consequently, the study provides a more comprehensive clinical profile of PFHBII, which may assist clinicians to identify other South African families or individuals with this potentially life-threatening disorder.

References

1. Brink AJ, Torrington M. Progressive familial heart block – two types. *S Afr Med J* 1977; **52**: 53–59.
2. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; **58**: 1072–1083.
3. Josephson ME, Marchlinski FE, Buxton AE. The bradyarrhythmias. In: Wilson JD, Braunwald E, Isselbacher KJ, Peteresdorf RG, Martin JB, Fauci AS, Root RK, eds. *Principles of Internal Medicine*. New York: McGraw-Hill, 1991: 902–908.
4. Fatkin D and Graham RM. Molecular mechanisms of inherited cardiomyopathies. *Physiol Rev* 2002; **82**: 945–980.
5. Fatkin D, MacRae C, Sasaki T, *et al*. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 1999; **341**: 1715–1724.
6. Jung M, Poepping I, Perrot A, *et al*. Investigation of a family with autosomal dominant dilated cardiomyopathy defines a novel locus on chromosome 2q14-q22. *Am J Hum Genet* 1999; **65**: 1068–1077.